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Research Article

Fungating and Non-Fungating Soft Tissue Sarcomas of the Extremities: Case Series and Modeling

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Abstract

Background: The potential role of fungation as a prognostic factor for soft tissue sarcoma is well established but its role is often confounded by other associated behavioural patterns, the analysis made difficult by small sample sizes and high histological heterogeneity.

Aims: To make use of a Bayesian Network, this can successfully account for both heterogeneity as well as small sample size, to evaluate the role of soft tissue sarcoma ulceration on patient prognosis.

Methods: This is a registry study. Retrospective data collection was performed using records of all sequential patients undergoing a surgical treatment after diagnostic confirmation of a soft tissue sarcoma of the lower or upper extremity, through a combination of diagnostic biopsy, and imaging exams discussed during regular interdisciplinary meetings. Each case was evaluated and a Bayesian Network model was built to evaluate the association between soft tissue sarcoma ulceration and patient prognosis.

Results: Synovial sarcoma was the most common soft tissue sarcoma. We observed a broad heterogeneity in tumor types, as such definition of prognosis for individual tumours was challenging. Although ulceration was not significantly associated with patient survival, ulceration had a direct impact on the probability of death (0.61), surpassing the impact of both recurrence (0.41) and complications (0.59).

Conclusions: Bayesian network holds promise in evaluating prognostic factors associated with ulceration, potentially serving as the basis for future personalised decision support systems.

Keywords: Soft tissue sarcoma; Prognosis; Bayesian Network; Ulceration; Fungating

Introduction

Soft-tissues are the most common site for sarcomas, with more than one case being diagnosed in the United States every hour and one person dying from this condition every two hours [1]. Despite having a high mortality rate, soft-tissue sarcomas are highly heterogeneous, with over 50 distinct subtypes identified to date [2]. As a consequence, evidence regarding their behaviour and treatment is sparse at best, most of the literature thus far having focused on descriptive case series that add little in terms of cumulative knowledge.

Primary therapy is predicated on surgical resection with negative margins [3], followed by radiation therapy depending on its subtype [4]. Limb-sparing surgery for extremity lesions is possible in most cases, with amputation being mainly reserved for more severe cases in terms of tumor size, predicted loss of limb function and neuro-vascular bundle invasion. Local recurrence rate ranges from 5% to up to 20%, with metastasis and subsequent mortality occurring in up to a third of all patients. Given the heterogeneity of these tumours and the low frequencies of individual diagnosis, most treatment guidelines rely on external tumor characteristics that might indicate its underlying aggressiveness. One such characteristic is the presence of fungation, as histologically high-grade tumours have been associated with bigger recurrence, metastasis rate [5], and mortality. Although ulcers have been deemed important when planning a soft-tissue sarcoma resection and subsequent limb reconstruction, to our knowledge no previous reports have demonstrated a specific association between ulceration and outcomes.

In face of this gap in knowledge regarding the clinical path of soft-tissue sarcomas, the aim of this article is to present a case series evaluated from a clinical, exploratory graphical analysis as well as through a Bayesian Network perspective.

Materials and Methods

This study was approved by the Institutional Review Board (IRB) of the University Sao Paulo, Brazil. The study design was retrospective, consequently, informed consent was not sought.

Study design

This is a registry study, where we have combined data retrospectively collected from 44 patient's records with a diagnosis of upper or lower limb soft tissue sarcoma.

Setting

All procedures took place between January 2010 and December

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Table 1: Sample characteristics by ulceration.

	Total (N=44)	No ulceration (N=34)	Ulceration (N=10)	p value
Female	25 (56.8%)	22 (64.7%)	3 (30.0%)	0.15
Age at surgery	45.9?? 18.7	43.4?? 17.5	54.7?? 20.8	0.238
Diagnosis				0.947
- Alveolar	2 (4.5%)	2 (5.9%)	0 (0.0%)	
- Spindle cell	5 (11.4%)	4 (11.8%)	1 (10.0%)	
- Leiomyosarcoma	3 (6.8%)	2 (5.9%)	1 (10.0%)	
- Liposarcoma	6 (13.6%)	5 (14.7%)	1 (10.0%)	
- Nerve sheath tumor	3 (6.8%)	2 (5.9%)	1 (10.0%)	
- Myxofibrosarcoma	3 (6.8%)	1 (2.9%)	2 (20.0%)	
- Pleomorphic spindle cell	3 (6.8%)	2 (5.9%)	1 (10.0%)	
- Pleomorphic rhabdomyosarcoma	1 (2.3%)	1 (2.9%)	0 (0.0%)	
- Pleomorphic sarcoma	6 (13.6%)	3 (8.8%)	3 (30.0%)	
- Sarcoma	2 (4.5%)	2 (5.9%)	0 (0.0%)	
- Synovial sarcoma	10 (22.7%)	10 (29.4%)	0 (0.0%)	
Procedure				0.116
- Amputation	11 (25.0%)	6 (17.6%)	5 (50.0%)	
- Resection	33 (75.0%)	28 (82.4%)	5 (50.0%)	
Extremity				0.659
- Lower	30 (68.2%)	22 (64.7%)	8 (80.0%)	
- Upper	14 (31.8%)	12 (35.3%)	2 (20.0%)	
Chemotherapy	26 (59.1%)	22 (64.7%)	4 (40.0%)	0.377
Flap				0.219
- Microsurgical	2 (4.5%)	2 (5.9%)	0 (0.0%)	
- Rotation	10 (22.7%)	5 (14.7%)	5 (50.0%)	
- No flap	32 (72.7%)	27 (79.4%)	5 (50.0%)	
Reconstruction	5 (11.4%)	5 (14.7%)	0 (0.0%)	0.436
Complication				0.966
- Cellulitis	1 (2.3%)	1 (2.9%)	0 (0.0%)	
- Collection	1 (2.3%)	1 (2.9%)	0 (0.0%)	
- Dehiscence	2 (4.5%)	1 (2.9%)	1 (10.0%)	
- Infection	9 (20.5%)	8 (23.5%)	1 (10.0%)	
- Luxation	1 (2.3%)	1 (2.9%)	0 (0.0%)	
- Necrosis	3 (6.8%)	1 (2.9%)	2 (20.0%)	
- Relapse	1 (2.3%)	1 (2.9%)	0 (0.0%)	
- No complication	26 (59.1%)	20 (58.8%)	6 (60.0%)	
Second procedure				0.816
- Cleaning	5 (11.4%)	4 (11.8%)	1 (10.0%)	
- Margin Expansion	1 (2.3%)	1 (2.9%)	0 (0.0%)	
- Resuture	1 (2.3%)	0 (0.0%)	1 (10.0%)	
- Skin Grafting	1 (2.3%)	1 (2.9%)	0 (0.0%)	
- Other	4 (9.1%)	2 (5.9%)	2 (20.0%)	
- No second procedure	32 (72.7%)	26 (76.5%)	6 (60.0%)	
Free Border	36 (81.8%)	28 (82.4%)	8 (80.0%)	0.986
Recurrence	7 (15.9%)	7 (20.6%)	0 (0.0%)	0.294
Reop secondary to recurrence	5 (11.4%)	5 (14.7%)	0 (0.0%)	0.436
Death	10 (22.7%)	8 (23.5%)	2 (20.0%)	0.973

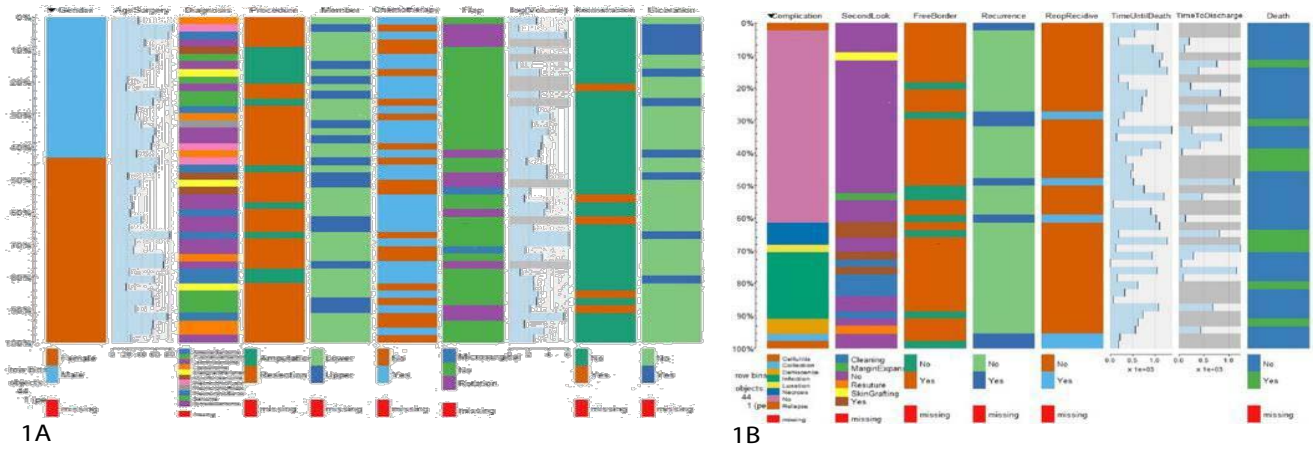

Figure 1(A,B): Exploratory graphical analysis for the study sample, distributed by ulceration status.

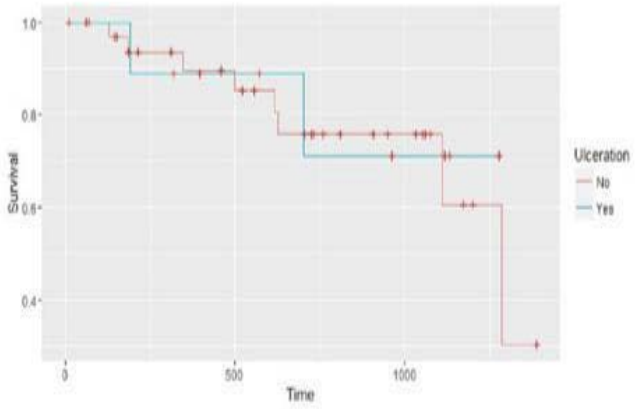

Figure 2: Survival plot by ulceration.

2013 at the Cancer Institute of the State of Sao Paulo (ICESP), a tertiary oncology hospital receiving referrals from all states in Brazil.

Participants

We included all sequential patients undergoing a surgical treatment after diagnostic confirmation of a soft tissue sarcoma of the lower or upper extremity through a combination of diagnostic biopsy and imaging exams discussed during regular interdisciplinary meetings. No other exclusion criteria were applied. Since this was a retrospective study, we used a combination of medical records and regular clinical appointments to obtain all data. Mortality status was individually ascertained by the hospital's medical records.

Variables

Each case was evaluated in relation to gender, age at surgery, diagnosis (alveolar, spindle cell, leiomyosarcoma, liposarcoma, nerve sheath tumor, myxofibrosarcoma, pleomorphic spindle cell, pleomorphic rhabdomyosarcoma, pleomorphic sarcoma, synovial sarcoma), procedure (amputation or resection), extremity (affected limb), chemotherapy, use of flaps (microsurgical, rotation), fungation, reconstruction, complication (cellulitis, abscess, dehiscence, infection, limb dislocation, necrosis, relapse), second procedure (cleaning, margin expansion, resuture, skin grafting, other), free border, recurrence, reoperation secondary to recurrence and death.

Data analysis

The analysis started with a descriptive graphical analysis, with continuous variables assessed for statistical distribution and variance. Categorical variables were evaluated for their frequency and percentage as well as for near zero categorical variance [6]. Near zero variance is particularly important in that it might degrade model performance. Therefore, a case by case decision was made to merge similar variable categories in presence of near zero variation.

A Bayesian Network model [7,8] was built to evaluate the association among all variables, so that experiments could be performed in relation to ulceration. Since the overall sample size is small, structure was not directly inferred from data but from prior expert knowledge [9,10]. This structure was then used for parameter estimation for each node connection. Expert elicitation was led by the first author (LP), who generated a graph, or group of clinical concepts and connecting edges, based on variables judged to be central to the investigation of the impact of ulcerated tumor. This graph was later discussed with co-authors using a Delphi method variant [11]. All participants are dedicated orthopaedic oncology surgeons. Specifically, an attempt was made not to unnecessarily increase graph complexity since this would generate convergence issues in our model. Score computation was performed using the following algorithms: Akaike Information Criterion, Gaussian log-likelihood Bayesian Information Criterion, K2 and Bayesian Dirichlet equivalent. In addition, our model was based on discrete variables, also with the objective of decreasing complexity. All analyses were conducted using the blearn package [12] within the R statistical language [13], additional packages including ggplot2 [14], tabplot [15], knitr [16], moon Book [17] and survival [18].

Results and Discussion

Participants

Patients consisted of 25 women and 19 men, ranging from 19 to 83 years old at the time of surgery, and with an average of 45.9 years of age. Diagnosis was highly heterogeneous, with synovial sarcoma being the most common. Most patients had tumours located on the lower extremity, undergoing resection with neither amputation nor reconstruction. In most cases we were able to achieve a free border, with neither a need for a re-operation nor recurrence (Table 1, Figure

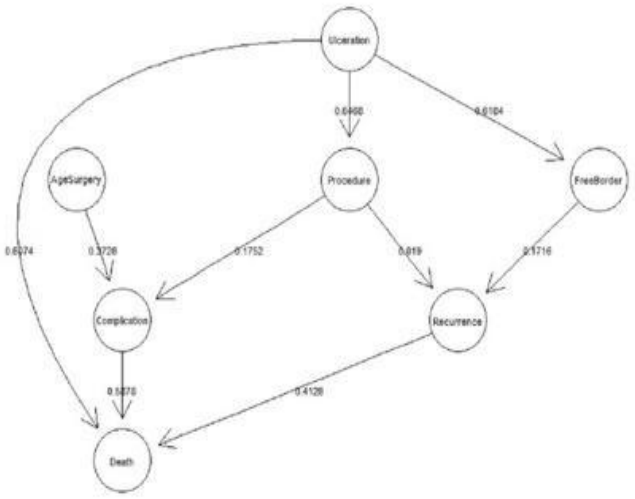

Figure 3: Bayesian model structure and parameters.

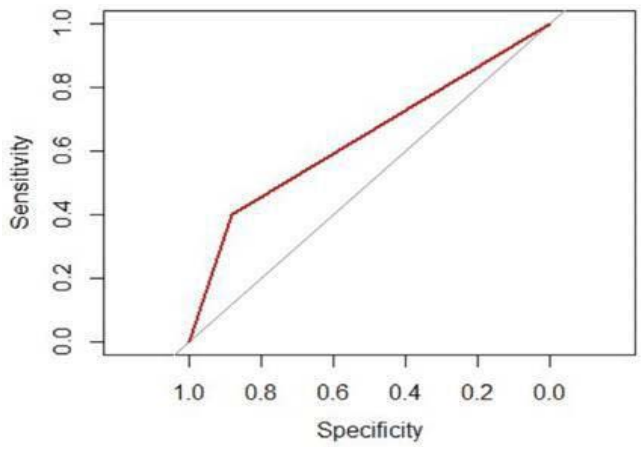

Figure 4: ROC for the Bayesian Network model.

1). When evaluating the unadjusted survival comparison between the presence and absence of ulceration on a Kaplan-Meier plot, no statistically significant difference was found between the two groups (p= 0.856, Figure 2).

Bayesian network modeling

Figure 3 displays the graph structure determined through expert opinion, with parameters inferred from our data. The model achieves a multi class area under the curve of 0.64 (Figure 4), which can be classified as fair. Important findings from this model include a direct impact of ulceration and the probability of death (0.61), surpassing the impact of both recurrence (0.41) and complications (0.59). Given that the percentage of cases with ulceration cannot be altered in this case mix, we then performed experiments to determine whether changes in our procedures could have affected our probabilities of mortality, recurrence or postoperative complications (Table 2).

Discussion

To the best of our knowledge, this is one of the first studies adding information on soft tissues sarcomas to a Bayesian Network, the only other exception being Brennan et al. [19], and the first Bayesian

Table 2: Experiments comparing amputation versus resection for death, recurrence and any type of complication.

Outcomes	Total	Amputation	Resection
Death	0.38	0.42	0.37
Recurrence	0.31	0.32	0.31
Complication	0.55	0.53	0.55
	Total	Amputation	Resection
No	0.6181985	0.5778409	0.6333325
Yes	0.3818015	0.4221591	0.3666675
	Total	Amputation	Resection
No	0.6869949	0.6805556	0.6894097
Yes	0.3130051	0.3194444	0.3105903
	Total	Amputation	Resection
Cellulitis	0.052686	0.0113636	0.0681818
Collection	0.0030992	0.0113636	0
Dehiscence	0.0416667	0.0113636	0.0530303
Infection	0.1890496	0.1477273	0.2045455
Luxation	0.0030992	0.0113636	0

Network model specifically focusing on the role of ulceration. We have found a broad heterogeneity in tumor types, which makes it difficult to define prognosis for individual tumours. In our series, although ulceration was not significantly associated with patient survival, ulceration did have a direct impact on the probability of death (0.61), surpassing the impact of both recurrence (0.41) and complications (0.59).

The literature on ulcerated soft tissue tumours is sparse. In one previous study, adjusted regression models demonstrated that disease stage, fungating lesions and size beyond 10 centimeters were all prognostic predictors of increased mortality rates [20]. These findings are consistent with the biology of these lesions, as they are believed to be more aggressive. Indirect signs of aggression could therefore be connected to worse outcomes. For example, previous studies have connected soft tissue tumors' metastatic patterns, intra-tumoral necrosis, and invasiveness with lower survival [21-26]. Similar results were obtained by using both the US National Cancer Institute (NCI) and the French Federation of Cancer Centres Sarcoma Group (FNCLCC) data to examine a cohort of patients with soft-tissue sarcomas [27].

Although lymph node metastases are not always present at the diagnosis of extremity soft-tissue sarcoma, patients presenting with isolated regional lymph node metastases have been reported to have better prognosis compared to those presenting with regional and distant metastases. Also synchronous regional lymph node metastases with the primary tumor have been reported to have a poorer outcome than metachronous isolated regional lymph node metastases in the absence of distant metastases [28]. Tumor invasiveness was found to be a significant prognostic indicator, as also reported in a 33-years retrospective study of children under 17 with synovial sarcoma [22] as well as another study involving 200 patients, in which the follow three features were investigated; tumor size, vascular invasion and tumor necrosis [29]. From this study, large tumor size and high histological grade were found to be independent adverse prognostic

factors for distant metastasis. Similar findings were obtained from a study on modified staging system of extremity soft-tissue sarcomas. Also in relation to local spread, recurrence is generally not a sign of a favourable prognosis, patients with a local recurrence of a soft tissue sarcoma being known to have a poor prognosis [30].

Given that margins are important, there seem to be no apparent difference in recurrence risk between amputation and limb salvage in the management of soft tissue limb sarcomas [30] partial hand preservation in the treatment of selected patients with large tissue sarcomas of the hand resulted in low local recurrence rates, good overall survival and limb functional outcome when negative resection margins are achieved [31]. As a result, some authors now recommend attempting to perform limb salvage surgery instead of amputation. However, the surgical method chosen should be influenced by the post treatment quality of life, life expectancy and survival of the patient [32]. Interestingly there seemed to be no significant difference between sarcoma patients requiring a complex reconstruction procedure and those treated by isolated resection methods [32]. While managing soft-tissue sarcomas of the limbs, it is important to consider possible post surgical oncological outcome as well as limb function. A study of soft-tissue sarcomas of the foot and ankle revealed that unplanned surgery for these tumours often results in more aggressive surgery and/or adjuvant radiotherapy. This may impact the final oncological outcome without necessarily worsening limb function [33].

As can be seen from the above discussion, most of the evidence related to ulceration is difficult to distinguish given the variety of factors associated with prognosis of these tumours, including large tumor size, positive microscopic surgical margins and high histological grade having all been identified as increasing the risk of distant metastases [34]. Also intriguing is that some studies have reported no association between the risk of recurrence and amputation versus limb salvage [30]. In face of studies with relatively low sample sizes as well as a series of indirect factors pointing toward a variety of outcomes, modelling methods such as Bayesian networks emerge as a particularly interesting analytical perspective. Bayesian Networks are a relatively new data analysis methodology, one of its main creators having been awarded the Nobel award-equivalent in Computer Sciences [35]. This methodology is particularly interesting for soft tissue tumor given its ability to accommodate not only small sample sizes but also causal networks with multiple and complex associations as previously outlined [36]. One of the characteristics of this model is that, whenever previous models are made available, its knowledge can be cumulative. Although not involving the evaluation of ulceration as a prognostic factor, prognostic factors for soft tissue sarcomas have been previously evaluated using a large registry by Brennan et al. [19]. Unfortunately, however, since currently there are no public repositories to which these models can be contributed, at this point the knowledge is still sparse. Future efforts should therefore be focused on developing not only repositories where multi-institutional models can be deposited, but also focusing on ensuring that a consistent nomenclature is used to measure both predictor and outcome variables. Such system would allow for the development of decision support systems to better guide personalised practice conduct [37].

Although our study makes a novel contribution to the literature, it does have its limitations. First, our sample size is relatively small for individual histological types. This limitation is however not exclusive to our study, as this is a rare type of tumor, with only one previous large series [19]. Secondly, our sample is highly heterogeneous, with the clustering of different tumor types leading to a loss of the potential to individualize prognostic predictions. Once again, this limitation is not exclusive to our study, but typical of most if not all previous publications. Last, our registry has a series of non-prospective components. While this decreases the final quality of our data, given the rarity of such lesions, the initial cases were received before an electronic data capture system was logistically possible within our healthcare system.

Conclusion

Our study points toward a high heterogeneity in soft tissue tumours, ultimately leading toward sparse prognostic information. Our main contribution is pointing to the possibility of cumulative knowledge through the use of Bayesian Networks, ultimately accounting for the high degree of prognostic heterogeneity and allowing for the creation of a large, international registry that could serve as the basis to personalised prognostic prediction.

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